

UNITED STATES DISTRICT COURT FOR
THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC. and
BARR LABORATORIES, INC.,

Plaintiffs,

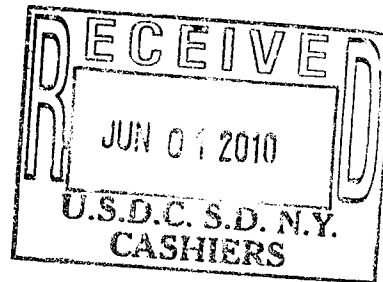
v.

BAYER SCHERING PHARMA AG and
BAYER HEALTHCARE
PHARMACEUTICALS INC.,

Defendants.

10 CIV 4340

Civil Action No. _____



COMPLAINT BY TEVA PHARMACEUTICALS USA, INC.
AND BARR LABORATORIES, INC. FOR DECLARATORY JUDGMENT

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*Counsel for Plaintiffs Teva Pharmaceuticals
USA, Inc. and Barr Laboratories, Inc.*

Plaintiffs Teva Pharmaceuticals USA, Inc. (“Teva”) and Barr Laboratories, Inc. (“Barr”) hereby complain of Defendants Bayer Schering Pharma AG and Bayer Healthcare Pharmaceuticals Inc. (“Bayer”), and allege as follows:

JURISDICTION AND VENUE

1. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

2. This Court has subject matter jurisdiction over this action under the Declaratory Judgments Act, 28 U.S.C. § 2201.

3. On information and belief, this Court has personal jurisdiction over Bayer inasmuch as Bayer is doing business in this State and District, and it has significant contacts with this State and District.

4. On May 28, 2010, Teva commenced sales of Gianvi™, which is a generic formulation of Bayer’s Yaz® product. This generic product was approved by the United States Food and Drug Administration on March 30, 2009.

5. By its June 1, 2010 news article (Exhibit 1), Bayer is quoted as saying it will file an infringement suit against Plaintiffs related to Plaintiffs’ launch of a generic version of Bayer’s Yaz® birth control drug. Bayer stated: “We believe this constitutes an act of infringement on intellectual property.” A copy of the news article is attached to the Complaint as Exhibit 1.

6. Plaintiffs contend that their launch of a generic formulation of the Yaz® product infringes no valid patent claim. There is, therefore, a dispute between Bayer and Plaintiffs that is definite and concrete, that requires the resolution of specific factual and legal issues as to which Bayer and Plaintiffs take different views, and that admits of specific relief through a judgment of

a conclusive character. Accordingly, there is subject matter jurisdiction under Article III of the Constitution and 28 U.S.C. §2201.

7. Venue is proper under 28 U.S.C. § 1391(b) and (c), and § 1400(b).

PARTIES

8. Plaintiff Teva is a corporation organized and existing under the laws of the state of Delaware with its principal place of business in North Wales, Pennsylvania.

9. Plaintiff Barr is a corporation organized and existing under the laws of the State of Delaware with its principal place of business at 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey. Barr is an indirect, wholly owned subsidiary of Teva.

10. On information and belief, Defendant Bayer Schering Pharma AG, formerly known as Schering AG, is a corporation organized and existing under the laws of the Federal Republic of Germany, having a principal place of business at Müllerstrasse 178, 13353 Berlin, Germany.

11. On information and belief, Defendant Bayer HealthCare Pharmaceuticals Inc., formerly known as Berlex, Inc., is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 340 Changebridge Road, P.O. Box 1000, Montville, New Jersey 07045-1000.

PATENTS-IN SUIT

12. United States Reissue Patent No. 37,838 (“the ‘838 reissue patent”), entitled Composition for Contraception, is attached to the Complaint as Exhibit 2. Inventors Jürgen Spona, Bernd Düsterberg, and Frank Lüdicke filed their application for this patent on February 15, 2000. The ‘838 reissue patent was issued September 10, 2002. On information and belief, Bayer is the current owner of the ‘838 reissue patent. The ‘838 reissue patent is listed in the

Orange Book for Yaz®. Bayer has asserted this patent against other pharmaceutical companies seeking to market a generic version of Yaz®.

13. United States Reissue Patent No. 37,564 (“the ‘564 reissue patent”), entitled Composition for Contraception, is attached to the Complaint as Exhibit 3. Inventors Jürgen Spona, Bernd Düsterberg, and Frank Lüdicke filed their application for this patent on February 15, 2000. The ‘564 reissue patent was issued February 26, 2002. On information and belief, Bayer is the current owner of the ‘564 reissue patent. The ‘564 reissue patent is listed in the Orange Book for Yaz®. Bayer has asserted this patent against other pharmaceutical companies seeking to market a generic version of Yaz®.

14. United States Reissue Patent No. 38,253 (“the ‘253 reissue patent”), entitled Composition for Contraception, is attached to the Complaint as Exhibit 4. Inventors Jürgen Spona, Bernd Düsterberg, and Frank Lüdicke filed their application for this patent on February 25, 2002. The ‘253 reissue patent was issued on September 16, 2003. On information and belief, Bayer is the current owner of the ‘253 reissue patent. The ‘253 reissue patent is listed in the Orange Book for Yaz®.

CLAIM ONE

(Declaratory Judgment of Invalidity and Noninfringement of the ‘838 Reissue Patent)

15. Plaintiffs incorporate Paragraphs 1-14 by reference.

16. Plaintiffs now seek a declaratory judgment pursuant to 28 U.S.C 2201(a) that the ‘838 reissue patent is invalid. Plaintiffs further seek a declaratory judgment pursuant to 28 U.S.C. 2201(a) that Plaintiffs do not infringe the ‘838 reissue patent.

17. A judicial declaration is necessary and appropriate at this time in order that Plaintiffs may ascertain their rights and duties with respect to the ‘838 reissue patent.

CLAIM TWO

(Declaratory Judgment of Invalidity and Noninfringement of the '564 Reissue Patent)

18. Plaintiffs incorporate Paragraphs 1-17 by reference.

19. Plaintiffs now seek a declaratory judgment pursuant to 28 U.S.C 2201(a) that the '564 reissue patent is invalid. Plaintiffs further seek a declaratory judgment pursuant to 28 U.S.C. 2201(a) that Plaintiffs do not infringe the '564 reissue patent.

20. A judicial declaration is necessary and appropriate at this time in order that Plaintiffs may ascertain their rights and duties with respect to the '564 reissue patent.

CLAIM THREE

(Declaratory Judgment of Invalidity and Noninfringement of the '253 Reissue Patent)

21. Plaintiffs incorporate Paragraphs 1-20 by reference.

22. Plaintiffs now seek a declaratory judgment pursuant to 28 U.S.C 2201(a) that the '253 reissue patent is invalid. Plaintiffs further seek a declaratory judgment pursuant to 28 U.S.C. 2201(a) that Plaintiffs do not infringe the '253 reissue patent.

23. A judicial declaration is necessary and appropriate at this time in order that Plaintiffs may ascertain their rights and duties with respect to the '253 reissue patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs request entry of judgment in its favor and against Defendants for:

FIRST CLAIM FOR RELIEF

- a. a declaration that the '838 reissue patent is invalid;
- b. a declaration that Plaintiffs do not infringe the '838 reissue patent;

- c. a permanent injunction against Defendants, their successors-in-interest, agents, representatives, and attorneys asserting or otherwise seeking to enforce the '838 reissue patent against Plaintiffs, their successors-in-interest, or any of their customers, dealers or suppliers, or any prospective or present sellers, dealers, distributors or customers;
- d. a finding that this case is exceptional under 35 U.S.C. § 285, and an award of attorney fees and costs of suit; and
- e. such other and further relief as may be appropriate.

SECOND CLAIM FOR RELIEF

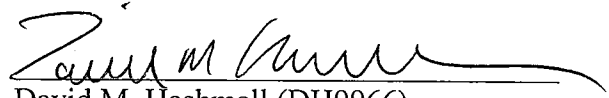
- a. a declaration that the '564 reissue patent is invalid;
- b. a declaration that Plaintiffs do not infringe the '564 reissue patent;
- c. a permanent injunction against Defendants, their successors-in-interest, agents, representatives, and attorneys asserting or otherwise seeking to enforce the '564 reissue patent against Plaintiffs, their successors-in-interest, or any of their customers, dealers or suppliers, or any prospective or present sellers, dealers, distributors or customers;
- d. a finding that this case is exceptional under 35 U.S.C. § 285, and an award of attorney fees and costs of suit; and
- e. such other and further relief as may be appropriate.

THIRD CLAIM FOR RELIEF

- a. a declaration that the '253 reissue patent is invalid;
- b. a declaration that Plaintiffs do not infringe the '253 reissue patent;

- c. a permanent injunction against Defendants, their successors-in-interest, agents, representatives, and attorneys asserting or otherwise seeking to enforce the '253 reissue patent against Plaintiffs, their successors-in-interest, or any of their customers, dealers or suppliers, or any prospective or present sellers, dealers, distributors or customers;
- d. a finding that this case is exceptional under 35 U.S.C. § 285, and an award of attorney fees and costs of suit; and
- e. such other and further relief as may be appropriate.

Dated: June 1, 2010



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EXHIBIT 1

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FRANKFURT (Dow Jones)

Bayer Schering Pharma AG said Tuesday it will file an infringement suit against Teva Pharmaceutical Industries Ltd. (TEVA), which is launching a generic version of Bayer's Yaz birth control drug in the U.S.

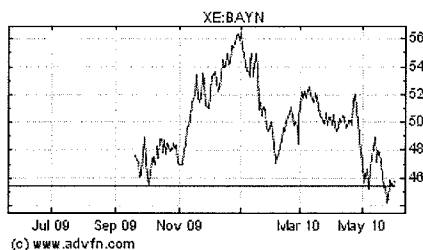
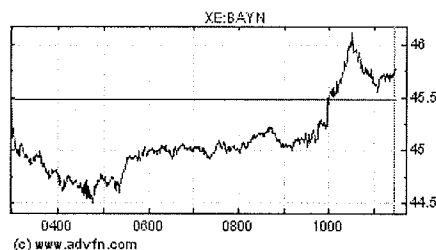
"We believe this constitutes an act of infringement on intellectual property," a spokesman for Bayer Schering Pharma said. "We will defend ourselves."

Teva said earlier Tuesday it has commercially launched Gianvi, a generic version of Yaz. The total sales of Yaz tablets in the U.S. were about \$782 million in 2009.

Bayer Schering Pharma is the pharmaceutical division of Germany's Bayer AG (BAYN.XE).

-By Sarah Sloat; Dow Jones Newswires; +49 69 29725521; sarah.sloat@dowjones.com

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Bayer Historical Chart**Bayer Intraday Chart**

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EXHIBIT 2

(19) **United States**
(12) **Reissued Patent**
Spona et al.

(10) **Patent Number:** **US RE37,838 E**
(45) **Date of Reissued Patent:** ***Sep. 10, 2002**

(54) **COMPOSITION FOR CONTRACEPTION**

(75) Inventors: **Jürgen Spona**, Vienna (AT); **Bernd Düsterberg**, Berlin (DE); **Frank Lüdicke**, Geneva (CH)

(73) Assignee: **Schering Aktiengesellschaft** (DE)

(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/504,084**

(22) Filed: **Feb. 15, 2000**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,824,667**
Issued: **Oct. 20, 1998**
Appl. No.: **08/742,147**
Filed: **Oct. 31, 1996**

U.S. Applications:

(63) Continuation of application No. 08/268,996, filed on Jun. 30, 1994, now Pat. No. 5,583,129.

(30) **Foreign Application Priority Data**

Dec. 22, 1993 (DE) 4344462

(51) **Int. Cl.⁷** **A61K 31/56**; A61K 31/57

(52) **U.S. Cl.** **514/170**

(58) **Field of Search** 514/170

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Primary Examiner—Phyllis G. Spivack

(57) **ABSTRACT**

A combination product for oral contraception is disclosed comprising an estrogen selected from 2.0 to 6.0 mg of 17β-estradiol and 0.020 mg of ethinylestradiol; and a gestagen selected from **[0.25 to 0.30 mg of]** drospirenone and **[0.1 to 0.2 mg of]** cyproterone acetate, followed by 5 or 4 pill-free or sugar pill days.

15 Claims, 1 Drawing Sheet

U.S. Patent

Sep. 10, 2002

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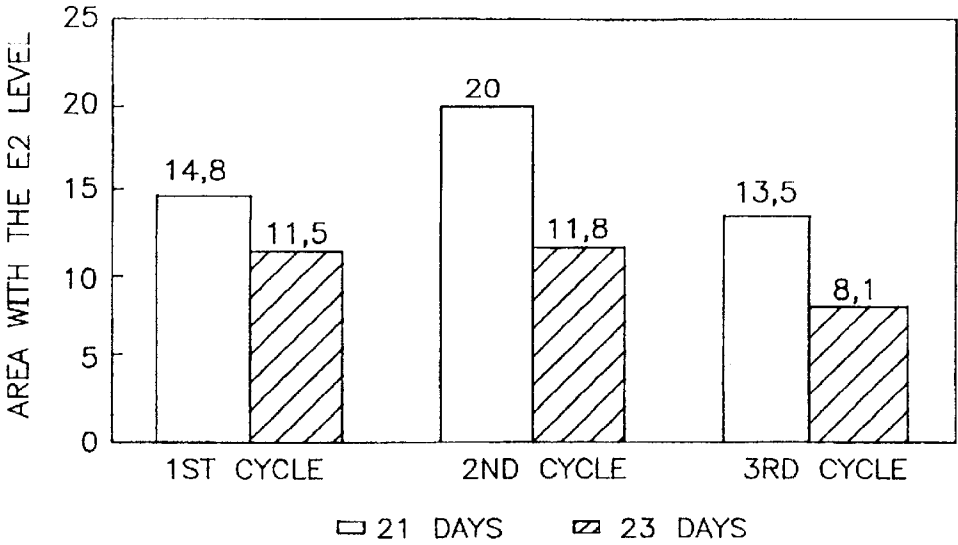


FIG. 1

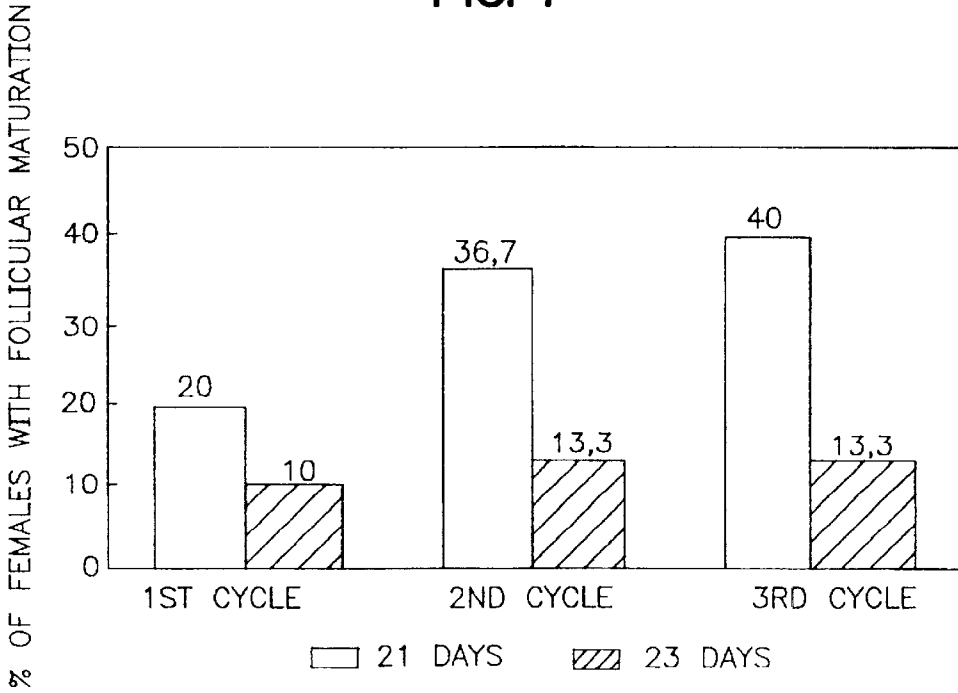


FIG. 2

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COMPOSITION FOR CONTRACEPTION

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

[This] *This reissue application is a continuation of Ser. No. 09/503,952 now RE37564, filed on even date; application Ser. No. 742,147, filed Oct. 31, 1996, now U.S. Pat. No. 5,824,667, which is a continuation of the application Ser. No. 08/268,996 filed Jun. 30, 1994, now U.S. Pat. No. 5,583,129.*

DESCRIPTION

This invention relates to the common use of estrogens and gestagens for the production of a combination preparation for oral contraception and a corresponding pack containing this combination preparation.

Combination preparations for oral contraception are already known, for example, Femovan® [DE-PS 2 546 062] or Marvelon® [DE-OS 2 361 120]. These preparations consist of 21 active ingredient-containing (estrogen/gestagen) dosage units and 7 active ingredient-free coated tablets (sugar pills; placebos). The dose to be administered daily is uniformly high in each case (so-called single-phase preparations) and produces the desired contraceptive effect in the entire intake period and in the intake pause or during the intake of the placebos. In most preparations, a 7-day interruption of the intake of active ingredient-containing dosage units was considered necessary until quite recently to trigger a reliable withdrawal bleeding and thus to achieve a satisfactory cycle control.

Other preparations, which exhibit more than 21 dosage units containing an estrogenic and progestational active ingredient, and in which the intake pause is partially (Ijzerman, Pasquale) or completely (Kuhl) bridged over by estrogen-containing dosage units. In this case, it is possible that the synthetic estrogen ethinylestradiol otherwise contained in oral contraceptives is replaced partially or completely by a conjugated estrogen, preferably estradiol.

A combination preparation for substitution therapy and contraception for females before menopause (approximately starting from the 40th year of life) is known from EP-A-0 253 607. This combination preparation contains an estrogen from the group

17 β -Estradiol,
ethinylestradiol and
mestranol

as well as a gestagen from the group

levonorgestrel,
gestodene,
desogestrel,
3-ketodesogestrel and
norethindrone.

A thus selected composition is to offset hormonal irregularities in the transition phase of premenopause and to help alleviate the symptoms caused by the hormonal changeover of the female organism in this phase. Such a composition simultaneously assures a premenopausal female the contraceptive protection still necessary at this age.

The development of new oral contraceptives for females of reproductive age before premenopause was characterized during the last twenty years above all by the reduction of the estrogen and gestagen dosages.

The reduction of the daily hormone dose was connected with the expectation to minimize the frequency of undesired

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side effects. Epidemiological data collected in the meantime confirm the desired trend toward better compatibility of lower-dosed preparations relative to cardiovascular complications [(1.) Thorogood, M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoeconomics and Drug Safety, Vol. 2: 3–16 (1993); (2.) Gerstman, B. B.; Piper, J. M.; Tomita, D. K.; Ferguson, W. J.; Stadel, B. V.; Lundin, F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol. 133, No. 1, 32–36 (1991); (3.) Lidegaard, O., Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956–63 (1993); (4.) Vessey, M.; Mant, D.; Smith, A.; Yeates, D.; Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292, (1986); (5.) Mishell, D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Suppl., 7–18 (1991)].

It is assumed that a correlation exists above all between the level of the estrogen dose and the incidence of cardiovascular diseases. But the maintenance of the contraceptive effectiveness stands in the way of an extreme reduction of the daily estrogen dose. Although the ovulation-inhibiting effect of the low-dosed oral contraceptives is caused mainly by the gestagenic component, the estrogenic component also makes a significant contribution to the central inhibition action and to the ovarian suppression (ovulation inhibition). Moreover, the daily estrogen dose must not fall below the minimum dose ranges, so that a satisfactory cycle control can be assured (Der Frauenarzt [The Gynecologist]; 34, 7: 793 (1993)).

The lowest estrogen dose contained in an oral contraceptive on the market at this time is 20 μ g of ethinylestradiol, combined with 150 μ g of desogestrel (Mercilon). Although the cycle control of this preparation is, as expected, somewhat poorer in comparison to preparations with a higher estrogen dose, the high acceptance rate of Mercilon indicates a small clinical relevance of this drawback. But the observation, made identically in several studies, of a lesser ovarian suppression of the preparation containing 20 μ g of ethinylestradiol represents a clinically important problem. Obviously with this very low estrogen dose, in the case of many females, the maturation of follicles, which could be detected with ultrasonic studies or hormonal studies, results [(6.) Lunell, N. O.; Carlström, K.; Zador, G.; Ovulation inhibition with a combined oral contraceptive containing 20 μ g of ethinylestradiol and 250 μ g of levonorgestrel; Acta. Obstet. Gynecol. Scand. Suppl. 88: 17–21 (1979); (7.) Mall-Haefeli, M.; Werner-Zodrow, I.; Huber, P. R.; Klinische Erfahrungen mit Mercilon und Marvelon unter besonderer Berücksichtigung der Ovar-Funktion [Clinical Experience with Mercilon and Marvelon under special consideration of the ovary function]; Geburtsh. und Frauenheilk. [Obstetrics and Gynecology] 51, 35–38, Georg Thieme Verlag, Stuttgart-New York (1991); (8.) Strobel, E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives]; Fortschr. Med. Vol. 110, No. 20 (1992); (9.) Letter to Editor, Contraception 45: 519–521 (1992); (10.) Teichmann, A. T.; Brill, K.; Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

The hormone determinations performed showed that functional granulosa cells that secrete 17 β -estradiol are involved. Each intake error in the case of females with clear ovarian activity, thus with follicular maturations, can result in a quick increase of gonadotropin production. The require-

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ments for an ovulation would thus be present. It is estimated that approximately one third of females take oral contraceptives irregularly within one year of use (Gynpress, Volume 1, No. 3, 1990). The risk of a pregnancy is therefore high especially in the case of intake errors with the 20 μg 5 ethinylestradiol preparations.

The object of this invention is an improved single-phase combination preparation for a female of reproductive age, who is not yet in premenopause, containing an estrogen and gestagen in each individual dosage unit, with the lowest possible estrogen content in each individual dosage unit, but also with a low total hormone content per administration cycle. 10

It has now been found that a pronounced ovarian suppression without frequent follicular maturations with low daily estrogen dosage, low total estrogen as well as low total hormone amount per administration cycle can be achieved by the use of a composition comprising an estrogen selected from 15

2.0 to 6.0 mg of 17 β -estradiol and
0.015 to 0.020 mg of ethinylestradiol;
and a gestagen selected from
0.05 to 0.075 mg of gestodene,
0.075 to 0.125 mg of levonorgestrel,
0.06 to 0.15 mg of desogestrel,
0.06 to 0.15 mg of 3-ketodesogestrel,
[0.1 to 0.3 mg of] drospirenone,
[0.1 to 0.2 mg of] cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
>0.35 to 0.75 mg of norethisterone.

for the production of a form of dosage for contraception for a female of reproductive age, who has not yet reached premenopause, by administration of the form of dosage for 23 or 24 days, beginning on day one of the menstrual cycle (first day of menstrual bleeding), followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle. 35

The terms "premenopause" and "menopause" are used within the scope of this invention in the meaning of the conventional definition, see, for example, "The Controversial Climacteric," P. A. of Keep et al., Ed., MTP press (1981), e.g., p. 9. 40

The daily hormone dose is kept to a very low level here, while the usual 21-day intake is extended by two or three days. The remaining 5 or 4 days of a cycle are preferably bridged over by placebos, to avoid intake errors, or by 5 or 4 intake-free days. 45

According to a preferred embodiment of this invention, this relates to the use of a composition comprising an estrogen selected from 50

>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
>0.06 to 0.075 mg of gestodene,
>0.100 to 0.125 mg of levonorgestrel,
>0.10 to 0.15 mg of desogestrel,
>0.10 to 0.15 mg of 3-ketodesogestrel,
0.25 to 0.30 mg of drospirenone,
[0.1 to 0.2 mg of] cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
0.50 to 0.75 mg of norethisterone

for the production of a form of dosage for contraception as described above.

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In addition, this invention relates to a combination product for oral contraception, which comprises

a) 23 or 24 dosage units, each containing an estrogen selected from
>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
>0.06 to 0.075 mg of gestodene,
>0.100 to 0.125 mg of levonorgestrel,
>0.10 to 0.15 mg of desogestrel,
>0.10 to 0.15 mg of 3-ketodesogestrel,
[0.25 to 0.30 mg of] drospirenone,
[0.1 to 0.2 mg of] cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
0.50 to 0.75 mg of norethisterone 15

and
b) 5 or 4 sugar pills or other indications to show that the daily administration of 23 or 24 dosage units is to be followed by 5 or 4 pill-free or sugar pill days are to be followed. 20

Further embodiments according to the invention follow from the features of the subclaims.

An especially preferred combination preparation according to this invention comprises 23 dosage units, each containing 20 μg of ethinylestradiol and 75 μg of gestodene and 5 sugar pills or other indications to show that no dosage unit or a sugar pill is administered during the last 5 days of the menstrual cycle. 25

The clinical study briefly described below was performed with ethinylestradiol as estrogen and gestodene as representative of the substance class of the gestagens possible according to the invention. All possible combinations of ethinylestradiol or estradiol according to the invention in the indicated dosages with one of the selected gestagens in the indicated dosages as 23- or 24-day preparations exhibit the advantages according to the invention. 30

The 23-day administration of 20 μg of ethinylestradiol in combination with 75 μg of gestodene results, in comparison to the 21-day administration a stronger ovarian suppression. In a double-placebo, randomized study on healthy females with normal ovarian function, groups of 30 test subjects each received the combination preparation either once daily over 21 or 23 days as well as placebos on 7 or 5 days (to assure the double-placebo nature of the study). 35

The treatment began after an ovulatory, untreated preliminary cycle on the first day of the menstrual bleeding of the subsequent cycle and extended altogether over three treatment cycles. The study was concluded with an untreated follow-up cycle. 40

The ovarian suppression was measured based on the level of the endogenous 17 β -estradiol level and the size of follicular structures. The results show that the 17 β -estradiol levels with 23-day intake of the test preparation were significantly lower ($p < 0.05$) in comparison to the 21-day administration (FIG. 1). 45

In accordance with this finding, the number of females with follicular maturations was also clearly higher in the 21-time administration relative to the 23-time administration (FIG. 2). 50

The intake interval extended only by two days surprisingly produces a significantly greater ovarian suppression with unchangingly low daily doses. The combination preparation according to the invention thus achieves the effectiveness previously known for preparations with a daily content of 30 μg of ethinylestradiol, although the daily ethinylestradiol dose is 33% lower and also the total dose per cycle is 27% lower. 55

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The advantages of a combination preparation for oral contraception to be administered over 23 days relative to the usual 21-day preparations with less than 30 µg of ethinylestradiol can be characterized as follows:

1. A significantly lower frequency of follicular developments in the user (maximum of 13% in females who received the 23-day preparation relative to a maximum of 40% among those who received the 21-day preparation). This means a greater contraceptive reliability of the 23-day preparation, especially in the case of previous intake errors. The danger of "breakthrough ovulations" is smaller.
2. The occurrence of large follicles of more than a 30 mm diameter is extremely rare. The development of ovarian cysts is improbable with the 23-day preparation in comparison to the 21-day preparation.
3. The recruitment of dominant follicles is suppressed in the shortened intake-free pause.
4. The endogenous 17β-estradiol levels are suppressed easily controllably in the case of the majority of the users of the 23-day preparation. Clinical symptoms such as breast tenseness, premenstrual syndrome and menstrual disorders; which can be attributed to increased and greatly fluctuating estrogen levels, are observed with the 23-day preparation with clearly lower frequency.

In summary, an intake, extended by two (or three) days, of preparations containing 20 µg of ethinylestradiol in each daily dosage unit can produce the above-mentioned advantages, without the daily dose having to be raised to the previously largely used level of 30 µg of ethinylestradiol.

The formulation of an estrogen and gestagen for the use according to the invention or for a combination preparation according to the invention takes place completely analogously as it is already known for usual oral contraceptives with 21-day intake period of the active ingredients, such as, for example, Femovang (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel).

A pack containing a combination preparation according to the invention is also designed analogously to packs for already known oral contraceptives on the market with the variation that instead of the usual 21 dosage units containing the active components, now 23 or 24 such dosage units and 5 or 4 sugar pills are present or else contain other suitable indications that 5 or 4 days are to be bridged over until continuation of the intake of active ingredient-containing dosage units.

Moreover, reference is made to the statements made in EP-A 0 253 607, especially also to the statements there for determination of equivalent amounts of ethinylestradiol and 17β-estradiol, on the one hand, and various gestagens, such as levonorgestrel, desogestrel, 3-ketodesogestrel and gestodene, on the other hand.

For further details for the determination of dose equivalents of various gestagenic active ingredients, reference is made to "Probleme der Dosisfindung: Sexualhormone" [Problems of Dose-Finding: Sex Hormones]; F. Neumann et al. in "Arzneimittelforschung" (Pharmaceutical Agent Research) 27, 2a, 296–318 (1977), as well as to "Aktuelle Entwicklungen in der hormonalen Kontrazeption" [Current Developments in Hormonal Contraception]; JH. Kuhl in Gyn akologe" [Gynecologist] 25: 231–240 (1992).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Area with the 17β-estradiol level in groups of 30 females, who are treated with an oral contraceptive (75 µg

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of gestodene+20 µg of ethinylestradiol) in 21- or 23-day administration interval over three cycles.

FIG. 2: Number of females in %, who showed follicular developments (>13 mm diameter) with 21- or 23-day treatment with an oral contraceptive (75 µg of gestodene+20 µg of ethinylestradiol).

We claim:

1. A combination product for oral contraception, comprising
(a) 23 or 24 dosage units, each containing an estrogen selected from
>2.0 to 6.0 mg of 17β-estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
[0.25 to 0.30 mg of] drospirenone and
[0.1 to 0.2 mg of] cyproterone acetate, in an amount which is equivalent to 75 µg of gestodene.
and
b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to be followed by 5 or 4, respectively pill-free or placebo pill days.
2. A combination preparation for oral contraception according to claim 1, wherein the estrogen is ethinylestradiol.
3. A combination preparation of claim 2, wherein the gestagen is cyproterone acetate.
4. A combination preparation of claim 2, wherein the gestagen is drospirenone.
5. A combination preparation according to claim 1, wherein the estrogen is present in a dose of 20 µg of ethinylestradiol or an equivalent dose of 17β-estradiol and the gestagen is present in a dose equivalent to 75 µg of [gestadene] gestodene.
6. A combination preparation according to claim 1, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.
7. A combination preparation according to claim 1, which comprises 23 dosage units, each containing 20 µg of ethinylestradiol and a dose of cyproterone acetate or drospirenone equivalent to 75 µg of gestodene and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.
8. A combination preparation of claim 1, wherein the estrogen is 17β-estradiol.
9. A combination preparation of claim 8, wherein the gestagen is cyproterone acetate.
10. A combination preparation of claim 8, wherein the gestagen is drospirenone.
11. A combination preparation of claim 4, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.
12. A combination preparation of claim 4, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

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13. A combination product for oral contraception, comprising

- (a) 23 or 24 daily dosage units, each containing 0.020 mg of ethinylestradiol, and an amount of drospirenone which is equivalent to 75 µg of gestodene, and
- (b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units, respectively, is to be followed by 5 or 4, respectively, pill-free or placebo pill days,

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wherein each of the dosage units containing drospirenone contains the same amount of drospirenone.

14. A combination preparation of claim 13, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

15. A combination preparation of claim 13, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

* * * * *

EXHIBIT 3



US00RE37564E

(19) **United States**
 (12) **Reissued Patent**
Spona et al.

(10) **Patent Number:** **US RE37,564 E**
 (45) **Date of Reissued Patent:** **Feb. 26, 2002**

(54) **COMPOSITION FOR CONTRACEPTION**

(75) Inventors: **Jürgen Spona**, Vienna (AT); **Bernd Düsterberg**, Berlin (DE); **Frank Lüdicke**, Geneva (CH)

(73) Assignee: **Schering Aktiengesellschaft**, Berlin (DE)

(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/503,952**

(22) Filed: **Feb. 15, 2000**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,824,667**
 Issued: **Oct. 20, 1998**
 Appl. No.: **09/742,147**
 Filed: **Oct. 31, 1996**

U.S. Applications:

(63) Continuation of application No. 08/268,996, filed on Jun. 30, 1994, now Pat. No. 5,583,129.

(30) **Foreign Application Priority Data**

Dec. 22, 1993 (DE) 43 44 462

(51) **Int. Cl.⁷** **A61K 31/57**; A61K 31/565

(52) **U.S. Cl.** **514/170**

(58) **Field of Search** 514/170

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Primary Examiner—Phyllis G. Spivack

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(57) **ABSTRACT**

A combination product for oral contraception is disclosed comprising an estrogen selected from

2.0 to 6.0 mg of 17β-estradiol and

0.020 mg of ethinylestradiol;

and a gestagen selected from

[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone and

[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,

followed by 5 or 4 pill-free or sugar pill days.

13 Claims, 1 Drawing Sheet

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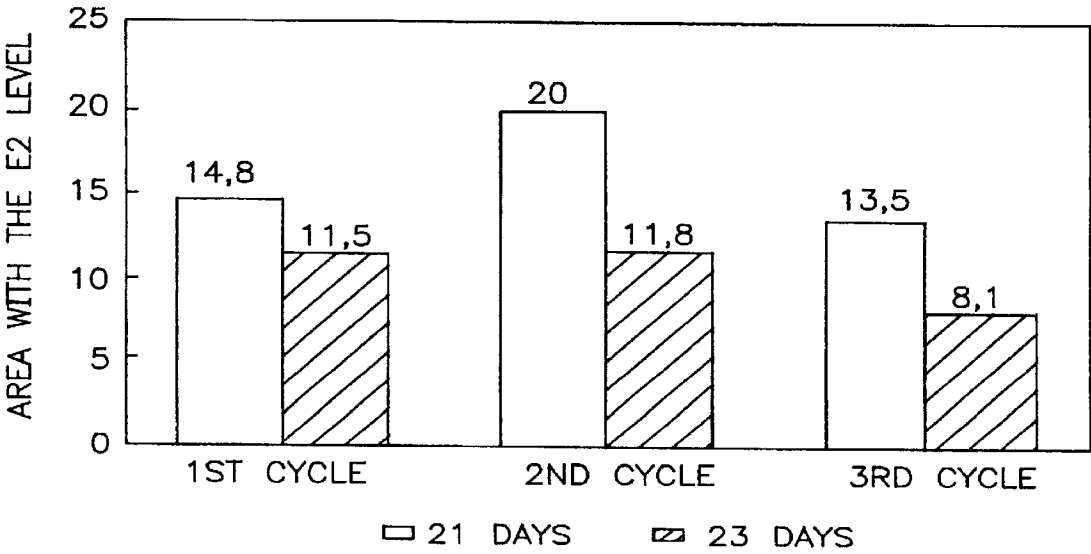


FIG. 1

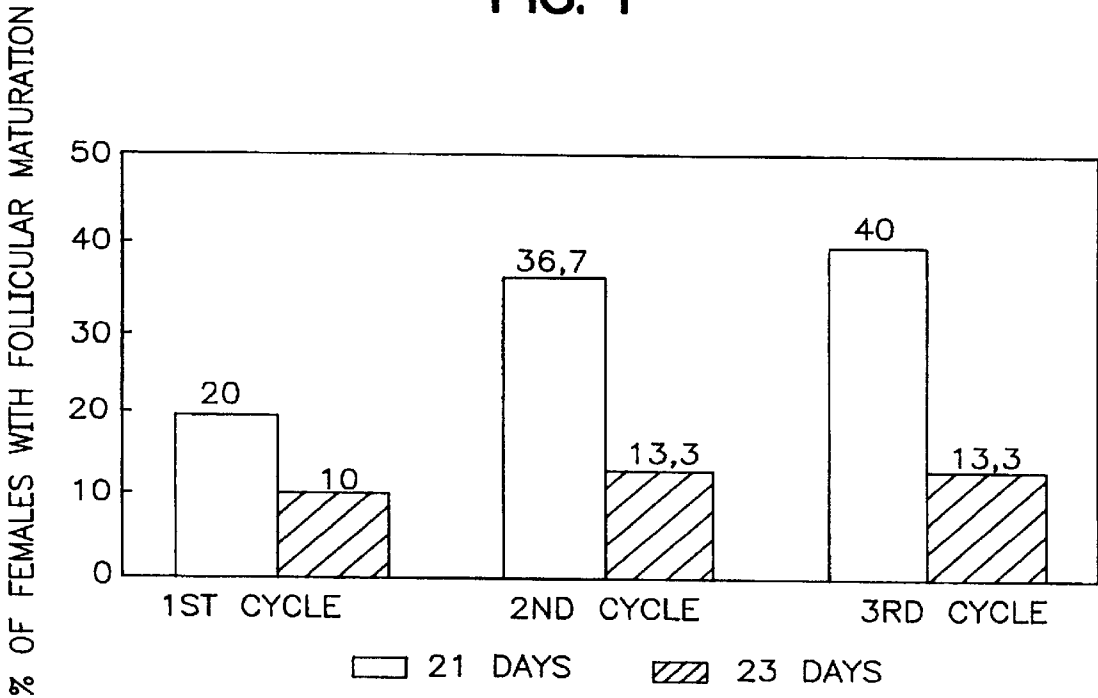


FIG. 2

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COMPOSITION FOR CONTRACEPTION

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

[This] *This application is the parent of application Ser. No. 09/504,084, both filed Feb. 15, 2000, both of which are reissues of application Ser. No. 08/742,147, filed Oct. 31, 1996, now U.S. Pat. No. 5,824,667, which is a continuation of the application Ser. No. 08/268,996 filed Jun. 30, 1994, now U.S. Pat. No. 5,583,129.*

DESCRIPTION

This invention relates to the common use of estrogen and gestagens for the production of a combination preparation for oral contraception and a corresponding pack containing this combination preparation.

Combination preparations for oral contraception are already known, for example, Femovan® [DE-PS 2 546 062] or Marvelon® [DE-OS 2 361 120]. These preparations consist of 21 active ingredient-containing (estrogen/gestagen) dosage units and 7 active ingredient-free coated tablets (sugar pills; placebos). The dose to be administered daily is uniformly high in each case (so-called single-phase preparations) and produces the desired contraceptive effect in the entire intake period and in the intake pause or during the intake of the placebos. In most preparations, a 7-day interruption of the intake of active ingredient-containing dosage units was considered necessary until quite recently to trigger a reliable withdrawal bleeding and thus to achieve a satisfactory cycle control.

Other preparations, which exhibit more than 21 dosage units containing an estrogenic and progestational active ingredient, and in which the intake pause is partially (Ijzerman, Pasquale) or completely (Kuhl) bridged over by estrogen-containing dosage units. In this case, it is possible that the synthetic estrogen ethinylestradiol otherwise contained in oral contraceptives is replaced partially or completely by a conjugated estrogen, preferably estradiol.

A combination preparation for substitution therapy and contraception for females before menopause (approximately starting from the 40th year of life) is known from EP-A-0 253 607. This combination preparation contains an estrogen from the group

17 β -Estradiol,
ethinylestradiol and
mestranol

as well as a gestagen from the group

levonorgestrel,
gestodene,
desogestrel,
3-ketodesogestrel and
norethindrone.

A thus selected composition is to offset hormonal irregularities in the transition phase of premenopause and to help alleviate the symptoms caused by the hormonal changeover of the female organism in this phase. Such a composition simultaneously assures a premenopausal female the contraceptive protection still necessary at this age.

The development of new oral contraceptives for females of reproductive age before premenopause was characterized during the last twenty years above all by the reduction of the estrogen and gestagen dosages.

The reduction of the daily hormone dose was connected with the expectation to minimize the frequency of undesired

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side effects. Epidemiological data collected in the meantime confirm the desired trend toward better compatibility of lower-dosed preparations relative to cardiovascular complications [(1.) Thorogood, M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoeconomics and Drug Safety, Vol. 2: 3–16 (1993); (2.) Gerstman, B. B.; Piper, J. M.; Tomita, D. K.; Ferguson, W. J.; Stadel, B. V.; Lundin, F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol. 133, No. 1, 32–36 (1991); (3.) Lidegaard, O., Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956–63 (1993); (4.) Vessey, M.; Mant, D.; Smith, A.; Yeates, D.; Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292, (1986); (5.) Mishell, D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Suppl., 7–18 (1991)].

It is assumed that a correlation exists above all between the level of the estrogen dose and the incidence of cardiovascular diseases. But the maintenance of the contraceptive effectiveness stands in the way of an extreme reduction of the daily estrogen dose. Although the ovulation-inhibiting effect of the low-dosed oral contraceptives is caused mainly by the gestagenic component, the estrogenic component also makes a significant contribution to the central inhibition action and to the ovarian suppression (ovulation inhibition). Moreover, the daily estrogen dose must not fall below the minimum dose ranges, so that a satisfactory cycle control can be assured (Der Frauenarzt [The Gynecologist]; 34, 7: 793 (1993)).

The lowest estrogen dose contained in an oral contraceptive on the market at this time is 20 μ g of ethinylestradiol, combined with 150 μ g of desogestrel (Mercilon). Although the cycle control of this preparation is, as expected, somewhat poorer in comparison to preparations with a higher estrogen dose, the high acceptance rate of Mercilon indicates a small clinical relevance of this drawback. But the observation, made identically in several studies, of a lesser ovarian suppression of the preparation containing 20 μ g of ethinylestradiol represents a clinically important problem. Obviously with this very low estrogen dose, in the case of many females, the maturation of follicles, which could be detected with ultrasonic studies or hormonal studies, results [(6.) Lunell, N. O.; Carström, K.; Zador, G.; Ovulation inhibition with a combined oral contraceptive containing 20 μ g of ethinylestradiol and 250 μ g of levonorgestrel; Acta. Obstet. Gynecol. Scand. Suppl. 88: 17–21 (1979); (7.) Mall-Haefeli, M.; Werner-Zodrow, I.; Huber, P. R.; Klinische Erfahrungen mit Mercilon und Marvelon unter besonderer Berücksichtigung der Ovar-Funktion [Clinical Experience with Mercilon and Marvelon under special consideration of the ovary function]; Geburtsh. und Frauenheilk. [Obstetrics and Gynecology] 51, 35–38, Georg Thieme Verlag, Stuttgart-New York (1991); (8.) Strobel, E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives]; Fortschr. Med. Vol. 110, No. 20 (1992); (9.) Letter to Editor, Contraception 45: 519–521 (1992); (10.) Teichmann, A. T.; Brill, K.; Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

The hormone determinations performed showed that functional granulosa cells that secrete 17 β -estradiol are involved. Each intake error in the case of females with clear ovarian activity, thus with follicular maturations, can result in a quick increase of gonadotropin production. The require-

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ments for an ovulation would thus be present. It is estimated that approximately one third of females take oral contraceptives irregularly within one year of use (Gynpress, Volume 1, No. 3, 1990). The risk of a pregnancy is therefore high especially in the case of intake errors with the 20 μ g 5 ethinylestradiol preparations.

The object of this invention is an improved single-phase combination preparation for a female of reproductive age, who is not yet in premenopause, containing an estrogen and gestagen in each individual dosage unit, with the lowest possible estrogen content in each individual dosage unit, but also with a low total hormone content per administration cycle.

It has now been found that a pronounced ovarian suppression without frequent follicular maturations with low daily estrogen dosage, low total estrogen as well as low total hormone amount per administration cycle can be achieved by the use of a composition comprising an estrogen selected from

2.0 to 6.0 mg of 17 β -estradiol and
0.015 to 0.020 mg of ethinylestradiol,
and a gestagen selected from
0.05 to 0.075 mg of gestodene,
0.075 to 0.125 mg of levonorgestrel,
0.06 to 0.15 mg of desogestrel,
0.06 to 0.15 mg of 3-ketodesogestrel,
[0.1 to 0.3] 1 to 3 mg of drospirenone,
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
>0.35 to 0.75 mg of norethisterone.

for the production of a form of dosage for contraception for a female of reproductive age, who has not yet reached premenopause, by administration of the form of dosage for 23 or 24 days, beginning on day one of the menstrual cycle (first day of menstrual bleeding), followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle.

The terms "premenopause" and "menopause" are used within the scope of this invention in the meaning of the conventional definition, see, for example, "The Controversial Climacteric," P. A. of Keep et al., Ed., MTP press (1981), e.g., p. 9.

The daily hormone dose is kept to a very low level here, while the usual 21-day intake is extended by two or three days. The remaining 5 or 4 days of a cycle are preferably bridged over by placebos, to avoid intake errors, or by 5 or 4 intake-free days.

According to a preferred embodiment of this invention, this relates to the use of a composition comprising an estrogen selected from

>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
>0.06 to 0.075 mg of gestodene,
>0.100 to 0.125 mg of levonorgestrel,
>0.10 to 0.15 mg of desogestrel,
>0.10 to 0.15 mg of 3-ketodesogestrel,
[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone,
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
0.50 to 0.75 mg of norethisterone

for the production of a form of dosage for contraception as described above.

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In addition, this invention relates to a combination product for oral contraception, which comprises

a) 23 or 24 dosage units, each containing an estrogen selected from

>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
>0.06 to 0.075 mg of gestodene,
>0.100 to 0.125 mg of levonorgestrel,
>0.10 to 0.15 mg of desogestrel,
>0.10 to 0.15 mg of 3-ketodesogestrel,
[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone,
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
0.50 to 0.75 mg of norethisterone

and
b) 5 or 4 sugar pills or other indications to show that the daily administration of 23 or 24 dosage units is to be followed by 5 or 4 pill-free or sugar pill days are to be followed.

Further embodiments according to the invention follow from the features of the subclaims.

An especially preferred combination preparation according to this invention comprises 23 dosage units, each containing 20 μ g of ethinylestradiol and 75 μ g of gestodene and 5 sugar pills or other indications to show that no dosage unit or a sugar pill is administered during the last 5 days of the menstrual cycle.

The clinical study briefly described below was performed with ethinylestradiol as estrogen and gestodene as representative of the substance class of the gestagens possible according to the invention. All possible combinations of ethinylestradiol or estradiol according to the invention in the indicated dosages with one of the selected gestagens in the indicated dosages as 23- or 24-day preparations exhibit the advantages according to the invention.

The 23-day administration of 20 μ g of ethinylestradiol in combination with 75 μ g of gestodene results, in comparison to the 21-day administration, in a stronger ovarian suppression. In a double-placebo, randomized study on healthy females with normal ovarian function, groups of 30 test subjects each received the combination preparation either once daily over 21 or 23 days as well as placebos on 7 or 5 days (to assure the double-placebo nature of the study).

The treatment began after an ovulatory, untreated preliminary cycle on the first day of the menstrual bleeding of the subsequent cycle and extended altogether over three treatment cycles. The study was concluded with an untreated follow-up cycle.

The ovarian suppression was measured based on the level of the endogenous 17 β -estradiol level and the size of follicular structures. The results show that the 17 β -estradiol levels with 23-day intake of the test preparation were significantly lower ($p < 0.05$) in comparison to the 21-day administration (FIG. 1).

In accordance with this finding, the number of females with follicular maturations was also clearly higher in the 21-time administration relative to the 23-time administration (FIG. 2).

The intake interval extended only by two days surprisingly produces a significantly greater ovarian suppression with unchangingly low daily doses. The combination preparation according to the invention thus achieves the effectiveness previously known for preparations with a daily content of 30 μ g of ethinylestradiol, although the daily

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ethinylestradiol dose is 33% lower and also the total dose per cycle is 27% lower.

The advantages of a combination preparation for oral contraception to be administered over 23 days relative to the usual 21-day preparations with less than 30 µg of ethinylestradiol can be characterized as follows:

1. A significantly lower frequency of follicular developments in the user (maximum of 13% in females who received the 23-day preparation relative to a maximum of 40% among those who received the 21-day preparation). This means a greater contraceptive reliability of the 23-day preparation, especially in the case of previous intake errors. The danger of "breakthrough ovulations" is smaller.

2. The occurrence of large follicles of more than a 30 mm diameter is extremely rare. The development of ovarian cysts is improbable with the 23-day preparation in comparison to the 21-day preparation.

3. The recruitment of dominant follicles is suppressed in the shortened intake-free pause.

4. The endogenous 17β-estradiol levels are suppressed easily controllably in the case of the majority of the users of the 23-day preparation. Clinical symptoms such as breast tenderness, premenstrual syndrome and menstrual disorders, which can be attributed to increased and greatly fluctuating estrogen levels, are observed with the 23-day preparation with clearly lower frequency.

In summary, an intake, extended by two (or three) days, of preparations containing 20 µg of ethinylestradiol in each daily dosage unit can produce the above-mentioned advantages, without the daily dose having to be raised to the previously largely used level of 30 µg of ethinylestradiol.

The formulation of an estrogen and gestagen for the use according to the intention or for a combination preparation according to the invention takes place completely analogously as it is already known for usual oral contraceptives with 21-day intake period of the active ingredients, such as, for example, Femovan® (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel).

A pack containing a combination preparation according to the invention is also designed analogously to packs for already known oral contraceptives on the market with the variation that instead of the usual 21 dosage units containing the active components, now 23 or 24 such dosage units and 5 or 4 sugar pills are present or else contain other suitable indications that 5 or 4 days are to be bridged over until continuation of the intake of active ingredient-containing dosage units.

Moreover, reference is made to the statements made in EP-A 0 253 607, especially also to the statements there for determination of equivalent amounts of ethinylestradiol and 17β-estradiol, on the one hand, and various gestagens, such as levonorgestrel, desogestrel, 3-ketodesogestrel and gestodene, on the other hand.

For further details for the determination of dose equivalents of various gestagenic active ingredients, reference is made to "Probleme der Dosisfindung: Sexualhormone" [Problems of Dose-Finding: Sex Hormones]; F. Neumann et al. in "Arzneimittelforschung" (Pharmaceutical Agent Research) 27, 2a, 296-318 (1977), as well as to "Aktuelle Entwicklungen in der hormonalen Kontrazeption" [Current Developments in Hormonal Contraception]; H. Kuhl in Gynäkologe" [Gynecologist] 25: 231-240 (1992).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Area with the 17β-estradiol level in groups of 30 females, who are treated with an oral contraceptive (75 µg of gestodene+20 µg of ethinylestradiol) in 21- or 23-day administration interval over three cycles.

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FIG. 2: Number of females in %, who showed follicular developments (>13 mm diameter) with 21- or 23-day treatment with an oral contraceptive (75 µg of gestodene+20 µg of ethinylestradiol).

We claim:

1. A combination product for oral contraception, comprising

(a) 23 or 24 dosage units, each containing an estrogen selected from
>2.0 to 6.0 mg of 17β-estradiol and
0.020 mg of ethinylestradiol;

and a gestagen selected from
[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone and
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,

and
b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to be followed by 5 or 4, respectively pill-free or placebo pill days.

2. A combination preparation for oral contraception according to claim 1, wherein the estrogen is ethinylestradiol.

3. A combination preparation of claim 2, wherein the gestagen is cyproterone acetate.

4. A combination preparation of claim 2, wherein the gestagen is drospirenone.

[5. A combination preparation according to claim 1, wherein the estrogen is present in a dose of 20 µg of ethinylestradiol or an equivalent dose of 17β-estradiol and the gestagen is present in a dose equivalent to 75 µg of gestadene.]

6. A combination preparation according to claim 1, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

[7. A combination preparation according to claim 1, which comprises 23 dosage units, each containing 20 µg of ethinylestradiol and a dose of cyproterone acetate or drospirenone equivalent to 75 µg of gestodene and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.]

8. A combination preparation of claim 1, wherein the estrogen is 17β-estradiol.

9. A combination preparation of claim 8, wherein the gestagen is cyproterone acetate.

10. A combination preparation of claim 8, wherein the gestagen is drospirenone.

11. A combination preparation of claim 4, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

12. A combination preparation of claim 4, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

13. A combination product for oral contraception, comprising

(a) 23 or 24 daily dosage units, each containing
0.020 mg of ethinylestradiol, and
2.5 to 3.0 mg of drospirenone,
and

(b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units, respectively, is to be followed by 5 or 4, respectively, pill-free or placebo pill days,

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wherein each of the dosage units containing drospirenone contains the same amount of drospirenone.

14. A combination preparation of claim 13, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

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15. A combination preparation of claim 13, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

* * * * *

EXHIBIT 4

US00RE38253E

(19) **United States**
 (12) **Reissued Patent**
Spona et al.

(10) **Patent Number:** **US RE38,253 E**
 (45) **Date of Reissued Patent:** **Sep. 16, 2003**

(54) **COMPOSITION FOR CONTRACEPTION**

(75) Inventors: **Jürgen Spona**, Vienna (AT); **Bernd Düsterberg**, Berlin (DE); **Frank Lüdicke**, Geneva (CH)

(73) Assignee: **Schering Aktiengesellschaft**, Berlin (DE)

(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/080,617**

(22) Filed: **Feb. 25, 2002**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **Re. 37,564**
 Issued: **Feb. 26, 2002**
 Appl. No.: **09/503,952**
 Filed: **Feb. 15, 2000**

U.S. Applications:

(63) Continuation of application No. 09/503,952, filed on Feb. 15, 2000, now Pat. No. Re. 37,564, which is a continuation of application No. 08/268,996, filed on Jun. 30, 1994, now Pat. No. 5,583,129.

(30) **Foreign Application Priority Data**

Dec. 22, 1993 (DE) 43 44 462

(51) **Int. Cl.⁷** **A61K 31/57**; A61K 31/565

(52) **U.S. Cl.** **514/170**

(58) **Field of Search** 514/170

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(57) **ABSTRACT**

A combination product for oral contraception is disclosed comprising an estrogen selected from

2.0 to 6.0 mg of 17β-estradiol and

0.020 mg of ethinylestradiol;

and a gestagen selected from

[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone and

[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,

followed by 5 or 4 pill-free or sugar pill days.

2 Claims, 1 Drawing Sheet

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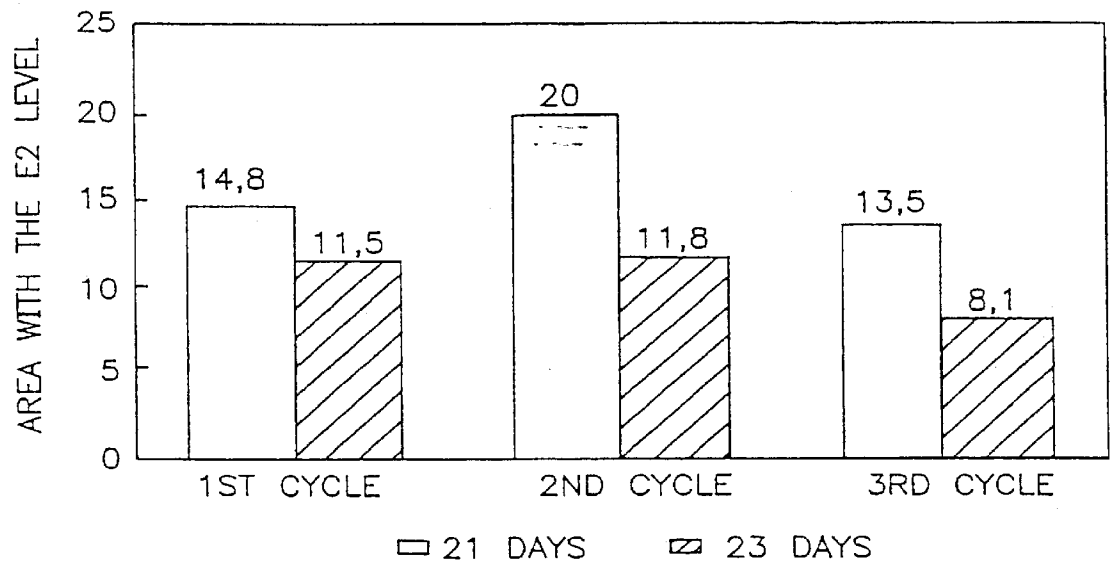


FIG. 1

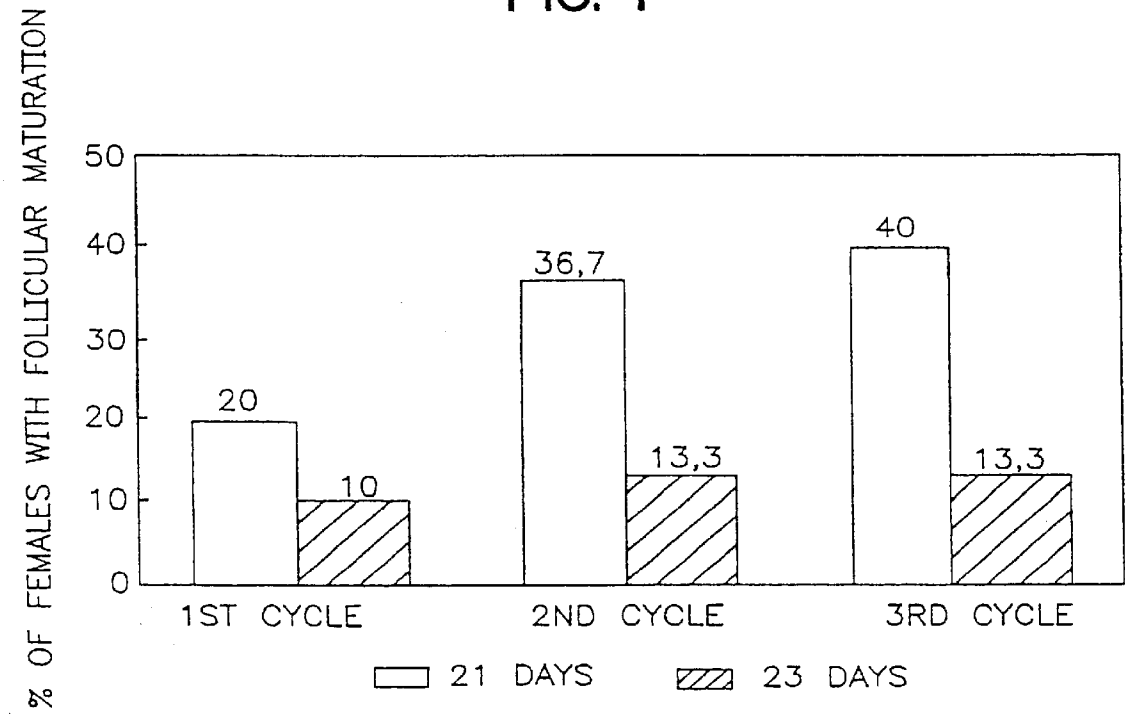


FIG. 2

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COMPOSITION FOR CONTRACEPTION

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This continuation reissue application is a continuation of reissue application Ser. No. 09/503,052, filed Feb. 15, 2000, now U.S. Pat. No. RE37,564 which is a reissue of application Ser. No. 08/742,147, filed Oct. 31, 1996, now U.S. Pat. No. 5,824,667, which is a continuation of the application Ser. No. 08/268,996 filed Jun. 30, 1994, now U.S. Pat. No. 5,583,129; Reissue Application Ser. No. 10/193,758 is a Continuation of Reissue Ser. No. 09/504,084, now U.S. Pat. No. RE37,838, which is a Divisional reissue application of Ser. No. 08/742,147, U.S. Pat. No. 5,824,667.

DESCRIPTION

This invention relates to the common use of estrogen and gestagens for the production of a combination preparation for oral contraception and a corresponding pack containing this combination preparation.

Combination preparations for oral contraception are already known, for example, Femovan® [DE-PS 2 546 062] or Marvelon® [DE-OS 2 361 120]. These preparations consist of 21 active ingredient-containing (estrogen/gestagen) dosage units and 7 active ingredient-free coated tablets (sugar pills; placebos). The dose to be administered daily is uniformly high in each case (so-called single-phase preparations) and produces the desired contraceptive effect in the entire intake period and in the intake pause or during the intake of the placebos. In most preparations, a 7-day interruption of the intake of active ingredient-containing dosage units was considered necessary until quite recently to trigger a reliable withdrawal bleeding and thus to achieve a satisfactory cycle control.

Other preparations, which exhibit more than 21 dosage units containing an estrogenic and progestational active ingredient, and in which the intake pause is partially (Ijzerman, Pasquale) or completely (Kuhl) bridged over by estrogen-containing dosage units. In this case, it is possible that the synthetic estrogen ethinylestradiol otherwise contained in oral contraceptives is replaced partially or completely by a conjugated estrogen, preferably estradiol.

A combination preparation for substitution therapy and contraception for females before menopause (approximately starting from the 40th year of life) is known from EP-A-0 253 607. This combination preparation contains an estrogen from the group

17 β -Estradiol,
ethinylestradiol and
mestranol

as well as a gestagen from the group
levonorgestrel,
gestodene,
desogestrel,
3-ketodesogestrel and
norethindrone.

A thus selected composition is to offset hormonal irregularities in the transition phase of premenopause and to help alleviate the symptoms caused by the hormonal changeover of the female organism in this phase. Such a composition simultaneously assures a premenopausal female the contraceptive protection still necessary at this age.

The development of new oral contraceptives for females of reproductive age before premenopause was characterized

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during the last twenty years above all by the reduction of the estrogen and gestagen dosages.

The reduction of the daily hormone dose was connected with the expectation to minimize the frequency of undesired side effects. Epidemiological data collected in the meantime confirm the desired trend toward better compatibility of lower-dosed preparations relative to cardiovascular complications [(1.) Thorogood, M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoeconomics and Drug Safety, Vol. 2: 3-16 (1993); (2.) Gerstman, B. B.; Piper, J. M.; Tomita, D. K.; Ferguson, W. J.; Stadel, B. V.; Lundin, F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol. 133, No. 1, 32-36 (1991); (3.) Lidegaard, O., Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956-63 (1993); (4.) Vessey, M.; Mant, D.; Smith, A.; Yeates, D.; Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292, (1986); (5.) Mishell, D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Supp., 7-18 (1991)].

It is assumed that a correlation exists above all between the level of the estrogen dose and the incidence of cardiovascular diseases. But the maintenance of the contraceptive effectiveness stands in the way of an extreme reduction of the daily estrogen dose. Although the ovulation-inhibiting effect of the low-dosed oral contraceptives is caused mainly by the gestagenic component, the estrogenic component also makes a significant contribution to the central inhibition action and to the ovarian suppression (ovulation inhibition). Moreover, the daily estrogen dose must not fall below the minimum dose ranges, so that a satisfactory cycle control can be assured (Der Frauenarzt [The Gynecologist]; 34, 7: 793 (1993)).

The lowest estrogen dose contained in an oral contraceptive on the market at this time is 20 μ g of ethinylestradiol, combined with 150 μ g of desogestrel (Mercilon). Although the cycle control of this preparation is, as expected, somewhat poorer in comparison to preparations with a higher estrogen dose, the high acceptance rate of Mercilon indicates a small clinical relevance of this drawback. But the observation, made identically in several studies, of a lesser ovarian suppression of the preparation containing 20 μ g of ethinylestradiol represents a clinically important problem. Obviously with this very low estrogen dose, in the case of many females, the maturation of follicles, which could be detected with ultrasonic studies or hormonal studies, results [(6.) Lunell, N. O.; Carström, K.; Zador, G.; Ovulation inhibition with a combined oral contraceptive containing 20 μ g of ethinylestradiol and 250 μ g of levonorgestrel; Acta. Obstet. Gynecol. Scand. Suppl. 88: 17-21 (1979); (7.) Mall-Haefeli, M.; Werner-Zodrow, I.; Huber, P. R.; Klinische Erfahrungen mit Mercilon und Marvelon unter besonderer Berücksichtigung der Ovar-Funktion [Clinical Experience with Mercilon and Marvelon under special consideration of the ovary function]; Geburtsh. und Frauenheilk. [Obstetrics and Gynecology] 51, 35-38, Georg Thieme Verlag, Stuttgart-New York (1991); (8.) Strobel, E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives] Fortschr. Med. Vol. 110, No. 20 (1992); (9.) Letter to Editor, Contraception 45: 519-521 (1992); (10.) Teichmann, A. T.; Brill, K.; Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

The hormone determinations performed showed that functional granulosa cells that secrete 17 β -estradiol are

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involved. Each intake error in the case of females with clear ovarian activity, thus with follicular maturations, can result in a quick increase of gonadotropin production. The requirements for an ovulation would thus be present. It is estimated that approximately one third of females take oral contraceptives irregularly within one year of use (Gynpress, Volume 1, No. 3, 1990). The risk of a pregnancy is therefore high especially in the case of intake errors with the 20 μ g ethinylestradiol preparations.

The object of this invention is an improved single-phase combination preparation for a female of reproductive age, who is not yet in premenopause, containing an estrogen and gestagen in each individual dosage unit, with the lowest possible estrogen content in each individual dosage unit, but also with a low total hormone content per administration cycle.

It has now been found that a pronounced ovarian suppression without frequent follicular maturations with low daily estrogen dosage, low total estrogen as well as low total hormone amount per administration cycle can be achieved by the use of a composition comprising an estrogen selected from

2.0 to 6.0 mg of 17 β -estradiol and
0.015 to 0.020 mg of ethinylestradiol,
and a gestagen selected from
0.05 to 0.075 mg of gestodene,
0.075 to 0.125 mg of levonorgestrel,
0.06 to 0.15 mg of desogestrel,
0.06 to 0.15 mg of 3-ketodesogestrel,
[0.1 to 0.3] 1 to 3 mg of drospirenone,
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
>0.35 to 0.75 mg of norethisterone.

for the production of a form of dosage for contraception for a female of reproductive age, who has not yet reached premenopause, by administration of the form of dosage for 23 or 24 days, beginning on day one of the menstrual cycle (first day of menstrual bleeding), followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle.

The terms "premenopause" and "menopause" are used within the scope of this invention in the meaning of the conventional definition, see, for example, "The Controversial Climacteric," P. A. of Keep et al., Ed., MTP press (1981), e.g., p. 9.

The daily hormone dose is kept to a very low level here, while the usual 21-day intake is extended by two or three days. The remaining 5 or 4 days of a cycle are preferably bridged over by placebos, to avoid intake errors, or by 5 or 4 intake-free days.

According to a preferred embodiment of this invention, this relates to the use of a composition comprising an estrogen selected from

>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
>0.06 to 0.075 mg of gestodene,
>0.100 to 0.125 mg of levonorgestrel,
>0.10 to 0.15 mg of desogestrel,
>0.10 to 0.15 mg of 3-ketodesogestrel,
[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone,
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
0.50 to 0.75 mg of norethisterone

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for the production of a form of dosage for contraception as described above.

In addition, this invention relates to a combination product for oral contraception, which comprises

a) 23 or 24 dosage units, each containing an estrogen selected from

>2.0 to 6.0 mg of 17 β -estradiol and

0.020 mg of ethinylestradiol;

and a gestagen selected from

>0.06 to 0.075 mg of gestodene,

>0.100 to 0.125 mg of levonorgestrel,

>0.10 to 0.15 mg of desogestrel,

>0.10 to 0.15 mg of 3-ketodesogestrel,

[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone,

[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,

0.2 to 0.3 mg of norgestimate and

0.50 to 0.75 mg of norethisterone

and

b) 5 or 4 sugar pills or other indications to show that the daily administration of 23 or 24 dosage units is to be followed by 5 or 4 pill-free or sugar pill days are to be followed.

Further embodiments according to the invention follow from the features of the subclaims.

An especially preferred combination preparation according to this invention comprises 23 dosage units, each containing 20 μ g of ethinylestradiol and 75 μ g of gestodene and 5 sugar pills or other indications to show that no dosage unit or a sugar pill is administered during the last 5 days of the menstrual cycle.

The clinical study briefly described below was performed with ethinylestradiol as estrogen and gestodene as representative of the substance class of the gestagens possible according to the invention. All possible combinations of ethinylestradiol or estradiol according to the invention in the indicated dosages with one of the selected gestagens in the indicated dosages as 23- or 24-day preparations exhibit the advantages according to the invention.

The 23-day administration of 20 μ g of ethinylestradiol in combination with 75 μ g of gestodene results, in comparison to the 21-day administration, in a stronger ovarian suppression. In a double-placebo, randomized study on healthy females with normal ovarian function, groups of 30 test subjects each received the combination preparation either once daily over 21 or 23 days as well as placebos on 7 or 5 days (to assure the double-placebo nature of the study).

The treatment began after an ovulatory, untreated preliminary cycle on the first day of the menstrual bleeding of the subsequent cycle and extended altogether over three treatment cycles. The study was concluded with an untreated follow-up cycle.

The ovarian suppression was measured based on the level of the endogenous 17 β -estradiol level and the size of follicular structures. The results show that the 17 β -estradiol levels with 23-day intake of the test preparation were significantly lower ($p < 0.05$) in comparison to the 21-day administration (FIG. 1).

In accordance with this finding, the number of females with follicular maturations was also clearly higher in the 21-time administration relative to the 23-time administration (FIG. 2).

The intake interval extended only by two days surprisingly produces a significantly greater ovarian suppression with unchangingly low daily doses. The combination preparation according to the invention thus achieves the effec-

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tiveness previously known for preparations with a daily content of 30 µg of ethinylestradiol, although the daily ethinylestradiol dose is 33% lower and also the total dose per cycle is 27% lower.

The advantages of a combination preparation for oral contraception to be administered over 23 days relative to the usual 21-day preparations with less than 30 µg of ethinylestradiol can be characterized as follows:

1. A significantly lower frequency of follicular developments in the user (maximum of 13% in females who received the 23-day preparation relative to a maximum of 40% among those who received the 21-day preparation). This means a greater contraceptive reliability of the 23-day preparation, especially in the case of previous intake errors. The danger of "breakthrough ovulations" is smaller.

2. The occurrence of large follicles of more than a 30 mm diameter is extremely rare. The development of ovarian cysts is improbable with the 23-day preparation in comparison to the 21-day preparation.

3. The recruitment of dominant follicles is suppressed in the shortened intake-free pause.

4. The endogenous 17β-estradiol levels are suppressed easily controllably in the case of the majority of the users of the 23-day preparation. Clinical symptoms such as breast tenseness, premenstrual syndrome and menstrual disorders, which can be attributed to increased and greatly fluctuating estrogen levels, are observed with the 23-day preparation with clearly lower frequency.

In summary, an intake, extended by two (or three) days, of preparations containing 20 µg of ethinylestradiol in each daily dosage unit can produce the above-mentioned advantages, without the daily dose having to be raised to the previously largely used level of 30 µg of ethinylestradiol.

The formulation of an estrogen and gestagen for the use according to the invention or for a combination preparation according to the invention takes place completely analogously as it is already known for usual oral contraceptives with 21-day intake period of the active ingredients, such as, for example, Femovan® (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel).

A pack containing a combination preparation according to the invention is also designed analogously to packs for already known oral contraceptives on the market with the variation that instead of the usual 21 dosage units containing the active components, now 23 or 24 such dosage units and 5 or 4 sugar pills are present or else contain other suitable indications that 5 or 4 days are to be bridged over until continuation of the intake of active ingredient-containing dosage units.

Moreover, reference is made to the statements made in EP-A 0 253 607, especially also to the statements there for determination of equivalent amounts of ethinylestradiol and 17β-estradiol, on the one hand, and various gestagens, such as levonorgestrel, desogestrel, 3-ketodesogestrel and gestodene, on the other hand.

For further details for the determination of dose equivalents of various gestagenic active ingredients, reference is made to "Probleme der Dosisfindung: Sexualhormone" [Problems of Dose-Finding: Sex Hormones]; F. Neumann et al. In "Arzneimittelforschung" (Pharmaceutical Agent Research) 27, 2a, 296-318 (1977), as well as to "Aktuelle Entwicklungen in der hormonalen Kontrazeption" [Current Developments in Hormonal Contraception]; H. Kuhl in Cyn äkologe" [Gynecologist] 25: 231-240 (1992).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Area with the 17β-estradiol level in groups of 30 females, who are treated with an oral contraceptive (75 µg

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of gestodene+20 µg of ethinylestradiol) in 21- or 23-day administration interval over three cycles.

FIG. 2: Number of females in %, who showed follicular developments (>13 mm diameter) with 21- or 23-day treatment with an oral contraceptive (75 µg of gestodene+20 µg of ethinylestradiol).

We claim:

[1. A combination product for oral contraception, comprising

(a) 23 or 24 dosage units, each containing an estrogen selected from >2.0 to 6.0 mg of 17β-estradiol and 0.020 mg of ethinylestradiol;

and a gestagen selected from 0.25 to 0.30 mg of drospirenone and 0.1 to 0.2 mg of cyproterone acetate,

and
b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to be followed by 5 or 4, respectively pill-free or placebo pill days.]

[2. A combination preparation for oral contraception according to claim 1, wherein the estrogen is ethinylestradiol.]

[3. A combination preparation of claim 2, wherein the gestagen is cyproterone acetate.]

[4. A combination preparation of claim 2, wherein the gestagen is drospirenone.]

5. A combination preparation [according to claim 1] for oral contraception, comprising,

(a) 23 or 24 dosage units, each containing an estrogen selected from ≤2.0 to 6.0 mg of 17β-estradiol and 0.020 mg of ethinylestradiol;

and a gestagen selected from 2.5 to 3.0 mg of drospirenone and 1 to 2 mg of cyproterone acetate,

and
b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to be followed by 5 or 4, respectively pill-free or placebo pill days,

wherein the estrogen is present in a dose of 20 µg of ethinylestradiol or an equivalent dose of 17β-estradiol and the gestagen is present in a dose equivalent to 75 µg of [gestadene] gestodene.

[6. A combination preparation according to claim 1, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days or the menstrual cycle.]

7. A combination preparation [according to claim 1] for oral contraception, comprising,

(a) 23 or 24 dosage units, each containing an estrogen selected from >2.0 to 6.0 mg of 17β-estradiol and 0.020 mg of ethinylestradiol;

and a gestagen selected from 2.5 to 3.0 mg of drospirenone and 1 to 2 mg of cyproterone acetate,

and
b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to

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be followed by 5 or 4, respectively pill-free or placebo pill days,
which comprises 23 dosage units, each containing 20 µg of ethinylestradiol and a dose of cyproterone acetate or drospirenone equivalent to 75 µg of gestodene and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

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- [8. A combination preparation of claim 1, wherein the estrogen is 17β-estradiol.]
- [9. A combination preparation of claim 8, wherein the gestagen is cyproterone acetate.]
- [10. A combination preparation of claim 8, wherein the gestagen is drospirenone.]

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